Remarks

The Applicants respectfully request entry of the proposed amendment by the Examiner. The amendments are believed to place the claims in condition for allowance. Additionally, the claims do not raise new issues that would require further consideration and/or search, they do not raise the issue of new matter, and there are no additional claims presented. Support for the amendments of claims 43, 65 and 86 are found on page 7, lines 13-16. The amendments to claims 37, 59, 80, 94 and 107 are merely rewording of the claim language and introduce no new matter.

Reconsideration of this Application is respectfully requested.

Upon entry of the foregoing amendment, claims 8 and 19-112 are pending in the application, with 21, 43, 65, 86 and 100-103 being the independent claims. Claims 8, 19 and 20 stand withdrawn by the Examiner. Claims 21-112 are under consideration. The Examiner stated in Paper No. 17 that claims 103-106, 108-112 were in condition for allowance; claims 25, 47, 67 68 and 72-75 were objected to for being dependent upon a rejected claim; and claims 21-24, 26-46, 48-66, 69-71, 76-102 and 107 stand rejected.

These changes are believed to introduce no new matter, and their entry is respectfully requested.

Based on the above amendment and the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding objections and rejections and that they be withdrawn.

Rejections under 35 U.S.C. § 112

The Examiner maintained the rejection of claims 37, 59, 80, 94 and 107 under 35 U.S.C. 112, second paragraph as being unclear. Although not in agreement with the Examiner, the Applicants nonetheless have amended the above-mentioned claims to advance prosecution. It is therefore believed that the claims overcome the concerns of the Examiner and request that the rejection be withdrawn.

The Examiner maintained the written description rejection of claims 21-24, 26-46, 48-66, 69-71, 76-102 and 107 under 35 U.S.C. 112, first paragraph. The Examiner stated on page three (3) of the Advisory Action that "the polynucleotide of claim 107, which is a deletion variant of the polynucleotide of claim 103, is not so limited to encoding a polypeptide having glucuronyl C5-epimerase activity." While not agreeing with the Examiner's position, the amendment to claim 107 should obviate this rejection and the rejection should be withdrawn.

The Examiner further states that "[t]he rejection of claims 21-24, 26-46, 48-66, 69-71, and 75-102 is maintained because, while the claims are limited to polynucleotides encoding polypeptides with glucuronyl C5-epimerase activity, the structures of the claimed polynucleotides have not been adequately described in the specification." The Applicants disagree. On page 13, lines 13-26 of the specification, discloses:

> "The cDNA structure indicates the occurrence of 3 potential N-glycosylation sites (the sequence listing). Sugar substituents may be important for the proper folding and catalytic activity of the enzyme, since the protein expressed in bacteria (which also gave a strong Western signal towards the polyclonal antibodies raised against the synthetic peptide; data not shown) was devoid of enzymatic activity. A potential transmembrane region is underlined in the sequence listing. The predicted protein contains two cystein residues, only one of which occurs in the isolated (truncated) protein. Since NEM was inhibitory to epimerase activity (data not shown), this single cystein unit may be essential to the catalytic mechanism."

Therefore, the Applicants have provided structural characteristics of the polypeptides encoded by the claimed polynucleotide have been described in the specification.

The Examiner further states that "[o]ne of skill in the art would recognize that the genus of polynucleotides of claim 21, encoding glucuronyl C5-epimerases having at least 95% identity to the peptides of parts (a)-(d) and (g)-(m) of claim 21 is not sufficient to describe the structures of the genus of claimed polynucleotides." The Applicants respectfully draw the attention of the Examiner to the Revised Interim Written Description Guidelines Training Materials (referred to herein as "the guidelines"), on page 54. Following the guidelines on page 54, the claims recites that the isolated polynucleotide encodes a glucuronyl C5-epimerase capable of converting D-glucuronic acid to L-iduronic acid, which activity can be established using the routine assay disclosed in the specification on page 14, lines 24 and bridging over to page 15, line 11. SEQ ID NO: 13. The Examiner has withdrawn all remaining art rejections, and thus the claimed polynucleotides are novel and unobvious. There is an actual reduction to practice of the claimed species in the originally filed sequences listing and enzymatic activities in Table II, for example. The claims recite that the claimed polynucleotide must encode an amino acid sequence with 95% identity to the recited amino acid sequences and have the claimed enzymatic activity. The guidelines then state that with the facts and claim language provided with the example, that "[o]ne of skill in the art would conclude that Applicant was in

possession of the necessary attributes possess by the members of the genus," and "[t]he disclosure meets the requirements of 35 U.S.C. § 112 first paragraph as providing adequate written description for the claimed invention." Applicants maintain that the specification provides at least as much written description support for the claimed polynucleotides as required by these guidelines.

The Examiner asserts that "one of skill in the art would recognize that the genus of polynucleotides encoding glucuronyl C5-epimerase of claims 43, 65, 79, 80 and 86 that hybridize under the recited low stringency conditions to polynucleotides encoding the peptides of parts (a)-(d) and (g)-(m) of claim 43 or hybridizes under the recited low stringency conditions to the polynucleotide fragments of parts (a) and (d)-(f) of claims 65, 79, and 80 or parts (a)-(c) of claim 86 are not sufficient to describe the structures of the genus of claimed polynucleotides. Provided the recited fragments, including internal deletions mutants of a polypeptide or polynucleotide, one of skill in the art would not be able to visualize or recognize the identity of the members of the genus of polynucleotides encoding glucuronyl C5-epimerases." The Examiner did not provide the basis upon which he determined the standard for the definition of "low stringency" and thus, the Applicants assert that the hybridization conditions stated in the claims meet the written description requirements. Nonetheless, in the interest of advancing prosecution, the amendment to the claims to replace "42^{0}C" with "65^{0}C" would fit the definition as described in the guidelines on page 35, Example 9 which defines "High stringency hybridization conditions" as "6XSSC and 65 degrees Celsius." The claims, as amended thus recite 6XSSC and 65^{0}C. It

is unclear to the Applicants why the Examiner included claim 80, since claim 80 does not recite hybridization language.

Regarding the statement by the Examiner that "[p]rovided the recited fragments, including internal deletion mutants of a polypeptide or polynucleotide, one of skill in the art would not be able to visualize or recognize the identity of the members of the genus of polynucleotides encoding glucuronyl C5-epimerase", the Applicants direct the attention of the Examiner to pages 4 and 5 of the specification which discloses:

> "As used herein the definition "glucuronyl C5-epimerase or a functional derivative thereof" refers to enzymes which have the capability of converting D-glucuronic acid to L-iduronic acid. Accordingly, the definition embraces all epimerases having such capability including functional variants, such as functional fragments, mutants resulting from mutageneses or other recombinant techniques.... "Functional derivatives" of the enzyme can include functional fragments, functional fusion proteins or functional mutant proteins. Such epimerases included in the present invention can have a deletion of one or more amino acids, such deletions being an N-terminal, C-terminal or internal deletions. Also truncated forms are envisioned as long as they have the conversion capability indicated herein.
>
> Operable fragments, mutants or truncated forms can be identified by screening. This is made possible by deletion of for example N-terminal, C-terminal or internal regions of the protein in a step-wise fashion, and the resulting derivative can be analyzed with regard to its capability of the desired conversion of D-glucuronic acid to L-iduronic acid."

The Applicants maintain that the scope of the claim encompasses only those polypeptides which have the stated activity, which was included in the claims, and thus, one of skill in the art would be able to visualize or recognize the members of the genus and easily be able to use the assays disclosed in the specification as routine as discussed *supra,* to determine whether the fragment or polypeptides with deletions fall within the genus. In response to the Examiner's comments that

the fragments are not of sufficient size such that one can visualize the identity of the member of the genus of polynucleotides encoding all polypeptide comprising the recited nucleotide or amino acid fragments, the Examiner has not provided either factual evidence or sound scientific reasoning to support his position. Additionally, it is clear from the wording of the claims that the Applicants do not intend to claim activity in just the recited sequences, but in a polynucleotide which encodes a polypeptide which comprises the stated sequences that have the stated enzymatic activity.

The Applicants maintain that the claim language and the supporting disclosure is clear to one of skill in the art and that the Applicants had possession of the invention at the time the application was filed.

The Examiner maintained the scope of enablement rejection under 35 U.S.C. § 112, paragraph 1 over claims 21-24, 26-46, 48-66, 69-71, 76-102 and 107. The amendment to Claim 107 clarifies that the claimed polynucleotide retains the stated enzymatic activity. Therefore, the concerns of the Examiner over claim 107 appears to be overcome. The Examiner also states that "Applicant's disclosure is *not* enabling for the scope of polynucleotides broadly encompassing *all* polynucleotides comprising a nucleotide sequence encoding a glucuronyl C5-epimerase having at least 95% identity to the peptides of parts (a)-(d) and (g)-(m) of claim 21, that hybridizes under the recited low stringency conditions to polynucleotides encoding the peptides of parts (a)-(d) and (g)-(m) of claim 43, hybridizes under the recited low stringency conditions to the polynucleotide fragments of parts (a) and (d)-(f) of claims 65, 79, and 80 or hybridizes under the

recited low stringency conditions to the polynucleotide fragments of parts (a)-(c) of claim 86 from any source, including internal deletion mutants." The Examiner adds that "Applicants have not disclosed the amino acids of the polypeptide of SEQ ID NO: 13 necessary to a catalytically active polypeptide having glucuronyl C5-epimerase catalytic activity.... Therefore, in addition to isolating the broad scope of the claimed polynucleotides, one of skill in the art must identify *all* amino acids of the polypeptide of SEQ ID NO: 13 required for glucuronyl C5-epimerase activity." [page 4 of Paper No. 17, emphasis added by the Examiner] The Applicant respectfully disagrees. The Applicant clarifies that the claims do not recite both hybridization of the claimed polynucleotides *and* a 95% identity to the stated sequences. It is not clear from the Examiner's comments if this was his interpretation of the claims. As indicated *supra*, the specification discloses "Sugar substituents may be important for the proper folding and catalytic activity of the enzyme, since the protein expressed in bacteria ... was devoid of enzymatic activity. A potential transmembrane region is underlined in the sequence listing. The predicted protein contains two cystein residues, only one of which occurs in the isolated (truncated) protein. Since NEM was inhibitory to epimerase activity (data not shown), this single cystein unit may be essential to the catalytic mechanism." (See page 13 and the sequence listing on pages 18 and 19) The Applicant has disclosed the entire sequence and the critical residues, transmembrane region and glycosylation patterns that are necessary for activity and demonstrated said activity. The Applicant believes that the specification properly enables the full scope of the claimed invention.

Using the analysis from *In re Wands*, 858 F.2d 731, 8 U.S.P.Q.2d 1400 (Fed. Cir. 1988) which states that enablement of a claimed invention must include an analysis of the following: 1) the quantity of experimentation necessary, 2) the amount of direction or guidance presented, 3) the presence or absence of working examples, 4) the nature of the invention, 5)the state of the prior art, 6) the relative skill of those in the art, 7) the predictability or unpredictability of the art, and 8) the breadth of the claims. The Applicant submits that the rejected claims are enabled for the full scope using the analysis of *In re Wands*. The assays necessary to determine the enzymatic activity of the claimed polynucleotides are disclosed to be routine, so the quantity of experimentation necessary to enable the claimed invention would not be undue. The Applicant has also provided guidance as to the full-length polynucleotide and polypeptide, along with disclosed fragments that are part of larger functioning polypeptides and assays which can be used to determine the presence and activity of the encoded polypeptide. The Applicant has provided working examples in enzymatic assays, antibody assays and provided sequences as discussed, *supra.* The enzymatic assays are routine and one of skill in the art, typically a person with at least a post baccalaureate education and several years of laboratory experience would be able to perform said assays using the specification and routine assays known in the art. Using the routine assays and the sequence and structural information in the specification, one of skill in the art would be able to easily determine and predict whether a given nucleic acid encoding a polypeptide would be a member of the claimed genus. Therefore, the

Applicant maintains that the claims are enabled for the reasons given above and submit that the claims are allowable.

Rejections under 35 U.S.C. § 102 and 35 U.S.C. § 103

It is gratefully acknowledged that the Examiner has withdrawn the rejection of claims 21, 31, 33, 38-40, 43, 53, 55 and 60-62 under 35 U.S.C. 102(b) over Wilson *et al.* (Nature *368:32-38*, 1994), and the rejection of claims 21, 43, 65 and 86 under 35 U.S.C. 102(b) over Voet *et al.* (*Biochemistry,* 2nd ed., John Wiley and Sons, Inc. 1995, page 966). Also, the Examiner has withdrawn the rejection of claims 86, 87, 90, 91 and 95-98 under 35 U.S.C. 102(b) and claim 99 under 35 U.S.C. 103(a) over Xue *et al.* (Cell *72:681-693*, 1993).

Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Advisory Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Supplemental Amendment and Reply is respectfully requested.

Respectfully submitted,

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Version with markings to show changes made

37.(Twice amended) [The] A polynucleotide of [claim 21] which encodes an amino acid sequence which has a deletion of the N-terminal, C-terminal or internal regions of the amino acid sequence encoded by the polynucleotide of claim 21, and wherein said amino acid sequence is selected from a member of the group consisting of SEQ ID Nos. 2, 3, 4, 5, 6, 7 and 8[, and wherein said polynucleotide encodes a polypeptide with a deletion of the N-terminal, C-terminal or internal regions].

43.(Twice amended) An isolated polynucleotide encoding a glucuronyl C5-epimerase capable of converting D-glucuronic acid to L-iduronic acid and which hybridizes under the conditions of incubation at [42] 65° C in a solution comprising: 6x SSC, 5x Denhardt's solution containing 0.1% SDS and 0.1 mg/ml denatured salmon sperm DNA, followed by washing in 2x SSC and 0.5% SDS at 42° C, to a polynucleotide encoding a polypeptide selected from the group consisting of:

(a) amino acids 1 to 45 of SEQ ID NO: 13;
(b) amino acids 25 to 45 of SEQ ID NO: 13;
(c) amino acids 74 to 86 of SEQ ID NO: 13;
(d) amino acids 77 to 97 of SEQ ID NO: 13;
(e) amino acids 25 to 444 of SEQ ID NO: 13;
(f) amino acids 1 to 444 of SEQ ID NO: 13;
(g) SEQ ID NO: 2;
(h) SEQ ID NO: 3;
(i) SEQ ID NO: 4;
(j) SEQ ID NO: 5;
(k) SEQ ID NO: 6;
(l) SEQ ID NO: 7 and
(m) SEQ ID NO: 8.

59.(Twice amended) [The] A polynucleotide [of claim 43,] which encodes an amino acid sequence which has a deletion of the N-terminal, C-terminal or internal regions of the amino acid sequence encoded by the polynucleotide of claim 43, and wherein said amino acid sequence is selected from a member of the group consisting of SEQ ID Nos. 2, 3, 4, 5, 6, 7 and 8[, and wherein said polynucleotide encodes a polypeptide with a deletion of the N-terminal, C-terminal or internal regions].

65.(Twice amended) An isolated polynucleotide, or an isolated complementary polynucleotide, which encodes a polypeptide having glucuronyl C5-epimerase activity and capable of converting D-glucuronic acid to L-iduronic acid, and which hybridizes under the conditions of incubation at [42] 65° C in a solution comprising: 6x SSC, 5x Denhardt's solution containing 0.1% SDS and 0.1 mg/ml

denatured salmon sperm DNA, followed by washing in 2x SSC and 0.5% SDS at 42° C, to said isolated polynucleotide selected from the group consisting of:

(a) nucleotides 73 to 207 of SEQ ID NO: 12;
(b) nucleotides 73 to 1404 of SEQ ID NO: 12;
(c) nucleotides 73 to 3085 of SEQ ID NO: 12;
(d) nucleotides 145 to 207 of SEQ ID NO: 12;
(e) nucleotides 292 to 329 of SEQ ID NO: 12;
(f) nucleotides 301 to 362 of SEQ ID NO: 12;
(g) nucleotides 145 to 1404 of SEQ ID NO: 12;
(h) nucleotides 145 to 3085 of SEQ ID NO: 12;
(i) nucleotides 1 to 1404 of SEQ ID NO: 12 and
(j) nucleotides 1 to 3085 of SEQ ID NO: 12[;].

80.(Twice amended) [The] A polynucleotide [claim 65,] which encodes an amino acid sequence which has a deletion of the N-terminal, C-terminal or internal regions of the amino acid sequence encoded by the polynucleotide of claim 65, and wherein said polynucleotide sequence is selected from a member of the group consisting of

(a) nucleotides 73 to 207 of SEQ ID NO: 12;
(b) nucleotides 73 to 1404 of SEQ ID NO: 12;
(c) nucleotides 73 to 3085 of SEQ ID NO: 12;
(d) nucleotides 145 to 207 of SEQ ID NO: 12;
(e) nucleotides 292 to 329 of SEQ ID NO: 12;
(f) nucleotides 301 to 362 of SEQ ID NO: 12;
(g) nucleotides 145 to 1404 of SEQ ID NO: 12;
(h) nucleotides 145 to 3085 of SEQ ID NO: 12;
(i) nucleotides 1 to 1404 of SEQ ID NO: 12 and
(j) nucleotides 1 to 3085 of SEQ ID NO: 12[;

and wherein said polynucleotide encodes a polypeptide with a deletion of the N-terminal, C-terminal or internal regions].

86.(Once amended) An isolated polynucleotide which encodes a polypeptide having glucuronyl C5-epimerase activity and capable of converting D-glucuronic acid to L-iduronic acid, or an isolated complementary polynucleotide, which hybridizes under the conditions of incubation at [42] 65° C in a solution comprising: 6x SSC, 5x Denhardt's solution containing 0.1% SDS and 0.1 mg/ml denatured salmon sperm DNA, followed by washing in 2x SSC and 0.5% SDS at 42° C, to said isolated polynucleotide or its complement, selected from the group consisting of:

(a) SEQ ID NO: 9;
(b) SEQ ID NO: 10 and
(c) SEQ ID NO: 11.

94.(Twice amended) [The] A polynucleotide [of claim 86,] which encodes an amino acid sequence which has a deletion of the N-terminal, C-terminal or internal regions of the amino acid sequence encoded by the polynucleotide of claim

86, and wherein said polynucleotide sequence is selected from a member of the group consisting of SEQ ID Nos: 9, 10 and 11 [and wherein said polynucleotide encodes a polypeptide with a deletion of the N-terminal, C-terminal or internal regions].

107.(Once amended) [The] A- polynucleotide [of claim 103,] which encodes an amino acid sequence which has a deletion of the N-terminal, C-terminal or internal regions of the amino acid sequence encoded by the polynucleotide of claim 103 [wherein said polynucleotide encodes a polypeptide with a deletion of the N-terminal, C-terminal or internal regions] and having glucuronyl C5-epimerase activity and capable of converting D-glucuronic acid to L-iduronic acid.